DURECT Corporation Announces Publication of Larsucosterol Phase 2b Results in NEJM Evidence

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The article presents new trial data, including subgroup analyses and liver biomarkers, which have guided the design of the Company's planned Phase 3 trial

CUPERTINO, Calif., Jan. 28, 2025 /PRNewswire/ — DURECT Corporation (Nasdaq: DRRX) today announced the publication of a peer-reviewed article on the AHFIRM trial data in *NEJM Evidence*. The full article, entitled, "Larsucosterol for the Treatment of Alcohol-Associated Hepatitis," can be accessed here.

The AHFIRM trial was a Phase 2b randomized, double-blind, placebo-controlled, international, multi-center study that evaluated the safety and efficacy of the Company's epigenetic modulator, larsucosterol, for the treatment of subjects with severe alcohol-associated hepatitis (AH). It enrolled 307 patients across three arms: placebo, which consisted of standard of care, with or without methylprednisolone capsules at the investigators' discretion, larsucosterol (30 mg) and larsucosterol (90 mg). A total of 62 centers enrolled patients including 46 US sites that enrolled 76% of patients. Topline results from AHFIRM were previously announced by DURECT.

"We are encouraged by the AHFIRM data and look forward to further assessing the benefits of larsucosterol in AH patients in a Phase 3 trial," said Dr. Mitchell Shiffman, Director of the Liver Institute of Virginia and lead study author. "Many marketed drugs and investigational agents have been evaluated for AH over decades, but none have proven consistently effective or received regulatory approval. Currently, a third of severe AH patients won't survive beyond three months. This patient community urgently needs a therapy that can improve standard of care and save lives."

Norman Sussman, MD, FAASLD, Chief Medical Officer of DURECT, commented, "The publication of the AHFIRM data in such an esteemed journal underscores the importance of the clinical findings — we are pleased to share the detailed results with the broader scientific and medical communities. Additional analyses in this article highlight regional differences in patient populations and in AH treatment regimens including time from hospital admission to treatment and the use of liver transplantation. This comprehensive analysis has guided us in designing a robust Phase 3 trial protocol to focus on U.S. patients, with 90-day mortality as the primary endpoint."

James E. Brown, D.V.M., President and CEO of DURECT, added, "We look forward to further demonstrating larsucosterol's potential in our upcoming Phase 3 trial. If successful, the Food and Drug Administraton (FDA) has agreed that a single Phase 3 trial could be sufficient to support a New Drug Application (NDA). We plan to initiate the trial in 2025, pending funding."

Key data highlights from the AHFIRM trial, include:

- Both the 30 mg and 90 mg larsucosterol doses demonstrated clinically meaningful trends in reducing 90-day mortality with mortality reductions of 41% (p=0.068) in the 30 mg arm and 35% (p=0.124) in the 90 mg arm compared with placebo.
- The reductions in mortality at 90 days were more pronounced in U.S. patients with reductions of 57% (p=0.014) in the 30 mg arm and 58% (p=0.008) in the 90 mg arm compared with placebo; computations for random sample analysis suggest that the U.S. results of larsucosterol treatment were unlikely to be an artifact of random chance.
- The numerical improvement in the primary endpoint of mortality or liver transplant at 90 days did not achieve statistical significance for either dose of larsucosterol.
- Variations in time from hospitalization to first dose highlighted the importance of timely treatment in patients with severe AH.
- Larsucosterol appeared safe and well tolerated in the AHFIRM trial and the number of treatment emergent adverse events (TEAEs) and newly-occurring significant complications of liver disease in both larsucosterol groups were similar to those in placebo.

About the AHFIRM Trial
AHFIRM was a Phase 2b randomized, double-blind, placebo-controlled, international, multi-center study conducted in subjects with severe alcohol-associated hepatitis (**AH**) to evaluate the sa**F**ety and eff**I**cacy of la**R**sucosterol treat**M**ent (AHFIRM). The study was comprised of three arms and enrolled 307 patients, with approximately 100 patients in each arm: (1) Placebo, which consisted of standard of care, with or without methylprednisolone capsules at the investigators' discretion; (2) larsucosterol (30 mg); and (3) larsucosterol (90 mg). Patients in the larsucosterol arms received the same supportive care without steroids. The primary outcome measure was the 90-day incidence of mortality or liver transplantation for patients treated with larsucosterol compared to those treated with placebo, and the key secondary endpoint was 90-day survival. The Company enrolled patients at clinical trial sites across the U.S., EU, U.K., and Australia. In November 2023, the Company announced topline data for the AHFIRM Trial. Reflecting the life-threatening nature of AH and the lack of therapeutic options, the U.S. Food and Drug Administration (FDA) has granted larsucosterol Fast Track Designation and Breakthrough Therapy Designation for the treatment of AH. For more information, refer to ClinicalTrials.gov Identifier: NCT04563026.

About Alcohol-associated Hepatitis (AH)
AH is an acute form of alcohol-associated liver disease (ALD) associated with long-term heavy alcohol intake, often following a recent period of increased consumption (i.e., a binge). AH is typically characterized by severe inflammation and liver cell damage, potentially leading to life-threatening complications including liver failure, acute kidney injury and multi-organ failure. There are no FDA approved therapies for AH, and a retrospective analysis of 77 studies published between 1971 and 2016, which included data from 8,184 patients, showed the overall mortality from AH was 26% at 28 days, 29% at 90 days and 44% at 180 days. A subsequent global study published in December 2021, which included 85 tertiary centers in 11 countries across 3 continents, prospectively enrolled 2,581 AH patients with a median Model of End-Stage Liver Disease (MELD) score of 23.5, reported mortality at 28 and 90 days of approximately 20% and 31%, respectively. Stopping alcohol consumption is necessary, but frequently not sufficient for recovery in many moderate (defined as MELD scores of 11-20) and severe (defined as MELD scores >20) patients, and therapies that reduce liver inflammation, such as corticosteroids, are limited by contraindications, have not been shown to improve survival at 90 days or one year, and have demonstrated an increased risk of infection. While liver transplantation is becoming more common for ALD patients, including AH patients, the total number of such transplants is relatively small, and limited by organ availability. Average charges for a liver transplant exceed $875,000, and patients require lifelong immunosuppressive therapy to prevent organ rejection.

About Larsucosterol
Larsucosterol is an endogenous sulfated oxysterol and an epigenetic modulator. Epigenetic regulators are compounds that regulate patterns of gene expression without modifying the DNA sequence. DNA hypermethylation, an example of epigenetic dysregulation, results in transcriptomic reprogramming and cellular dysfunction, and has been reported in many acute (e.g., AH) and chronic diseases (e.g., MASH). As an inhibitor of DNA methyltransferases (DNMT1, DNMT3a and 3b), larsucosterol inhibits DNA methylation, which subsequently modulates expression of genes that are involved in cell signaling pathways associated with stress responses, cell death and survival, and lipid biosynthesis. This may ultimately lead to improved cell survival, reduced inflammation, and decreased lipotoxicity. As an epigenetic modulator, the proposed mechanism of action provides further scientific rationale for developing larsucosterol for the treatment of acute organ injury and certain chronic diseases.

About DURECT Corporation
DURECT is a late-stage biopharmaceutical company pioneering the development of epigenetic therapies that target dysregulated DNA methylation to transform the treatment of serious and life-threatening conditions, including acute organ injury. Larsucosterol, DURECT's lead drug candidate, binds to and inhibits the activity of DNA methyltransferases, epigenetic enzymes that are elevated

and associated with hypermethylation found in AH patients. Larsucosterol is in clinical development for the potential treatment of AH, for which the FDA has granted a Fast Track and a Breakthrough Therapy designation; MASH is also being explored. In addition, POSIMIR® (bupivacaine solution) for infiltration use, a non-opioid analgesic utilizing the innovative SABER® platform technology, is FDA-approved. For more information about DURECT, please visit www.durect.com and follow us on X (formerly Twitter) at https://x.com/DURECTCorp.

DURECT Forward-Looking Statements

This press release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, relating to: our plans to conduct a Phase 3 clinical trial of larsucosterol, the ability of the Phase 3 trial, if successful, to support an NDA filing, the sufficiency of our capital requirements through the first half of 2025 and the potential uses of larsucosterol to treat patients with AH and potentially other indications. Actual results may differ materially from those contained in the forward-looking statements contained in this press release, and reported results should not be considered as an indication of future performance. The potential risks and uncertainties that could cause actual results to differ from those projected include, among other things, the risk that future clinical trials of larsucosterol are delayed or do not confirm the results from subset analyses of the AHFIRM trial, including geographic or other segmentation, or of earlier clinical or pre-clinical trials, or do not demonstrate the safety or efficacy of larsucosterol in a statistically significant manner; the risk that we do not raise sufficient capital to commence or complete the Phase 3 clinical trial of larsucosterol in patients with AH or continue to fund our operations, the risk that the FDA or other government agencies may require additional clinical trials for larsucosterol before approving larsucosterol for the treatment of AH, the risk that Breakthrough Therapy designation does not expedite the process for FDA approval and that larsucosterol may never be approved; and risks related to the sufficiency of our cash resources, our anticipated capital requirements, our ability to meet the minimum bid price for continued listing on Nasdaq, and our ability to continue to operate as a going concern. Further information regarding these and other risks is included in DURECT's most recent Securities and Exchange Commission filings, including its annual report on Form 10-K for the year ended December 31, 2023 and quarterly report on Form 10-Q for the quarter ended September 30, 2024, under the heading "Risk Factors." These reports are available on our website www.durect.com under the "Investors" tab and on the SEC's website at www.sec.gov. All information provided in this press release is based on information available to DURECT as of the date hereof, and DURECT assumes no obligation to update this information as a result of future events or developments, except as required by law.

NOTE: POSIMIR® is a trademark of Innocoll Pharmaceuticals, Ltd. in the U.S. and a trademark of DURECT Corporation outside of the U.S. SABER® is a trademark of DURECT Corporation. Other referenced trademarks belong to their respective owners. Larsucosterol is an investigational drug candidate under development and has not been approved for commercialization by the U.S. Food and Drug Administration or other health authorities for any indication.

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